A Protocol for the EBMT Solid Tumour Working Party
in collaboration with the German Cancer society AGO/AIO

HIDOC - European Intergroup Study

Formerly OVCAT

A RANDOMISED PHASE III TRIAL OF SEQUENTIAL HIGH DOSE CHEMOTHERAPY OR STANDARD DOSE CHEMOTHERAPY FOR OPTIMALLY DEBULKED FIGO STAGE III AND IV OVARIAN CANCER

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1. PROTOCOL SUMMARY & STUDY SCHEMA

Summary

Phase III trial of sequential high dose chemotherapy versus standard dose chemotherapy for advanced ovarian cancer.

Objectives

To compare the progression-free survival between high dose sequential and standard dose chemotherapy in patients with stage III or IV ovarian cancer. Secondary objectives are overall survival, quality of life and comparison of toxicity between the two groups.

Design

Prospective, multicentre, open and randomised comparison.

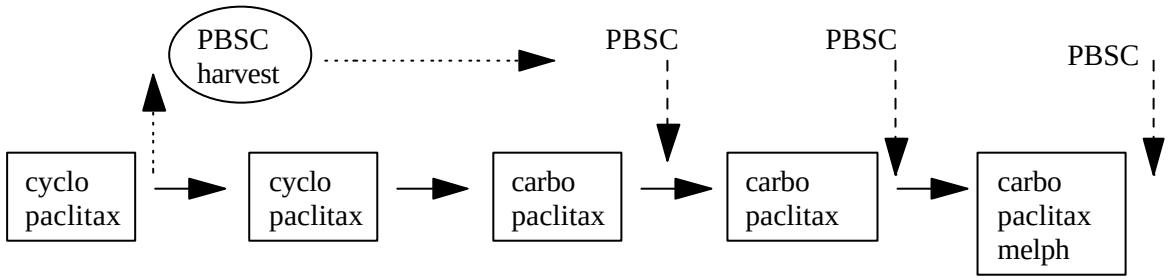
Sample Size

208 patients, 104 in each treatment group.

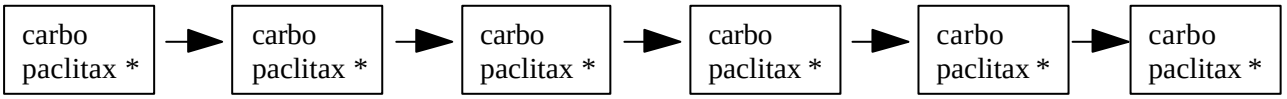
Eligibility

- FIGO stage III or IV epithelial ovarian cancer or cancer of the fallopian tubes
- Bilateral salpingo-oophorectomy, hysterectomy and omentectomy
- < 2cm disease maximum diameter after debulking surgery
- ≥ 18 years and ≤ 65 years
- No previous chemotherapy or radiotherapy
- Normal haematological, hepatic, renal and cardiac function
- Written informed consent

Regimen



versus



cyclo =cyclophosphamide / carbo=carboplatin / paclitax= paclitaxel / melph=melphalan

cisplatin may be substituted for carboplatin

* doxorubicin or epirubicin in addition, if standard in centre

Investigation summary

	Pre-treat	Pre-chemo cycles	Post-treatment Months 4-6 wks	3	6	9	12	15	18	21	24
Hist& Exam	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Wt/Perf Sc	X	X	X	X	X	X	X	X	X	X	X
FBC	X	X	X	X	X	-	X	-	-	-	X
Chemistry[d]	X	X	X	X	-	-	X	-	-	-	-
CA125	X	X	X	X	X	X	X	X	X	X	X
CT scan	X	-	-	X	-[b]	-[b]	-[b]	-[b]	-[b]	-[b]	-[b]
CXR	X	-	-[a]	-	-	-	-	-	-	-	-
GFR	X	X HD-see App4	-	X HD	-	-	-	-	-	-	-
ECG	X	-	-	-	-	-	-	-	-	-	-
Audiogram	X HD	-	-	X HD	-	-	-	-	-	-	-
QOL	X	-	X	X	-	X	-	X	-	-	-

[a]= unless previously abnormal

[b]= if CA125 raised or clinical suspicion of relapse

[c] = includes gynaecological assessment

[d] = creatinine, urea, electrolytes, liver function

HD = High-dose arm

Follow-up forms will be requested 3-monthly for 2 years, then 6-monthly until 5 years and annually thereafter until death.

2. INTRODUCTION

Epithelial ovarian cancer is a highly responsive tumour to platinum-based chemotherapy[1]. Nevertheless, the prognosis of advanced FIGO stage III and IV disease is poor with reported five year survival rates of 15-25%[2,3]. These disappointing long-term results are due to frequent relapses from therapy as the disease becomes more resistant. Cytotoxic chemotherapy with new agents such as taxanes have resulted in only a modest benefit in survival[4] and new therapeutic strategies are needed.

Preclinical studies have demonstrated a dose-response effect in many tumour types and it is now possible to test this in the clinic using bone marrow, haematopoeitic growth factors, and peripheral blood stem cells to support chemotherapy. Dose escalation has been shown to be beneficial in the treatment of some haematological tumours[5] and this approach may benefit patients with common solid tumours, such as breast cancer[6,7]. A preliminary analysis of blood and bone marrow transplant registry data suggests that high dose chemotherapy in ovary cancer may improve survival by about 10%[8,9].

2.1 PLATINUM DOSE-INTENSITY

In advanced ovarian cancer attempts to overcome emerging resistance have concentrated on platinum dose-intensification, largely based on a retrospective analysis by Levin and Hryniuk[10,11]. This demonstrated a statistically significant correlation between increasing dose-intensity of cisplatin and both response rate and overall survival.

There have been several randomised trials of platinum dose intensity performed over the past 5-10 years[12] but the merit of dose-intensive approaches in ovarian cancer remains unproven. One reason may be tumour bulk, which is an important independent prognostic variable. The majority of the studies were undertaken in patients with sub-optimally debulked disease; survival of this group following standard doses is consistently worse than in patients with minimal residual disease and the same may be true with higher dose therapy. In most studies the platinum dose has been increased no more than two-fold and data from animal models suggest that much higher doses need to be given to overcome resistance[13].

2.2 HIGH DOSE CHEMOTHERAPY REGIMENS IN RELAPSED OVARIAN CANCER

Early studies of high dose chemotherapy in ovarian cancer were performed using autologous bone marrow support in patients failing conventional treatment regimens. Dose-response relationships have been demonstrated in preclinical studies for alkylating drugs so that clinical trials have used agents such as melphalan, cyclophosphamide and thiotepa. These are active in ovarian cancer and can be substantially dose-escalated with the use of autologous bone marrow or peripheral blood stem cell support. There have been many phase I studies over the last 20 years but few have been of sufficient size to draw firm conclusions about the best way forward. Sphall et al[14] have summarised many of these early trials and concluded that the response rate to intensive chemotherapy in ovarian cancer refractory to standard doses of chemotherapy is high.

Stiff et al[15] have recently analysed their experience in 100 patients treated with high dose chemotherapy and autologous stem cell transplantation. Multivariate analysis demonstrated that platinum sensitivity and tumour bulk were the most important predictors of progression-free survival. The median overall survival times were 9.6 and 23.1 months for patients with platinum-resistant and sensitive disease. They concluded that patients with minimal residual disease and platinum sensitivity should be the group studied in future trials.

2.3 HIGH DOSE CHEMOTHERAPY REGIMENS IN PATIENTS WITH CHEMOSENSITIVE DISEASE

It has been generally accepted that the response of a tumour to standard therapy is a valuable predictor of response to subsequent high dose therapy. Mulder et al combined high dose cyclophosphamide with etoposide in patients with residual disease at second-look laparotomy. Complete responses were seen only in patients with minimal residual disease at second look laparotomy; 6 out of 8 patients in this group had a complete response which was confirmed as a pathological response in 5 patients(16). Both Viens et al (17) and Legros et al(18) have recently updated their experience with high dose melphalan, or more recently high dose carboplatin with either melphalan or cyclophosphamide in patients responding to first-line platinum-based chemotherapy. Both groups conclude the best results are seen in patients with small volume disease after initial platinum-based therapy. Legros et al reported a five year survival of 59.9% for the 53 patients treated and 23.6 % were disease-free. The group in clinical complete remission, of whom only 19 out of 31 had a pathological remission at second-look surgery had an overall five year survival of 71.2 % with 26.9 % disease-free at that time.

Short intensive chemotherapy has been used by Benedetti-Panici et al (19) in twenty chemo-naive patients with >0.5 cm residual disease. Two high dose platinum-based cycles were followed by bone marrow or stem cell supported therapy. Thirty-seven percent achieved a pathological complete remission at laparotomy 4-6 months later.

2.4 MULTICYCLE REGIMENS

Single consolidation high dose chemotherapy may not be the optimum approach as tumours may have already developed resistance so that a single dose of intensive chemotherapy is not sufficient to eradicate residual tumour. The early use of high dose treatment may reduce the emergence of resistant cells. n animal studies, higher doses of chemotherapy yield increased log cell kill and this is borne out in the clinical setting where the use of high dose chemotherapy has been capable of achieving significant tumour volume reduction. However, recurrence remains the rule, presumably due to failure to eradicate clones of highly-resistant cancer cells. In general, successful treatment programmes for chemotherapy-curable cancers have two features in common. The first is the availability of a regimen, which produces frequent complete responses. The second is the feasibility of delivering a minimum number of courses of that regimen in full doses. Peripheral blood stem cell supported therapy leads to a more rapid recovery of peripheral blood counts than autologous bone marrow transplantation. Cells can be collected after chemotherapy and re-infused after repeated administration of high dose chemotherapy.

The Memorial Sloan-Kettering Cancer Center have used a rapidly sequenced high dose chemotherapy regimen in a phase I/II study combining high dose induction therapy with paclitaxel and cyclophosphamide, followed by high dose carboplatin/paclitaxel, and a final cycle of high dose melphalan(20). Twelve out of 26 patients were able to complete all cycles and 5 out of 13 assessable patients (38.5%) had a complete pathological response.

A multiple sequential phase I/II study has recently been performed by Wandt and colleagues(21) in patients with previously untreated ovarian cancer. Twenty-one patients received induction therapy with high dose cyclophosphamide followed by two high dose cycles of carboplatin in escalating doses and finally carboplatin, etoposide and high dose melphalan. Treatment was given at 4 week intervals and all high dose cycles were supported by peripheral blood stem cell infusions and filgrastim post re-infusion. One group of 8 patients received paclitaxel 175 mg/m^2 with all therapies. Ototoxicity was dose-limiting (Grade 2; 50%) with the MTD for carboplatin being 1600mg/m^2 and there was no increase in toxicity by adding paclitaxel. Diarrhoea Grade 3 was found in up to 30% patients at some time during therapy and was readily controlled. Part of this treatment was successfully managed as outpatient therapy. Eleven patients (52%) achieved a complete response. The median progression-free survival is 25 months after a median follow up of 22.5 months (Wandt, unpublished data).

2.5 CONCLUSION

The evidence from registry data suggests a possible benefit from high dose intensive therapy. This now needs to be tested in a prospective, randomised phase III trial. This study incorporates the most active drugs in ovarian cancer, given sequentially and supported by peripheral blood stem cell therapy. The regimen is based on the pilot study performed by Wandt and colleagues. More than half of the patients treated with paclitaxel and platinum regimens, which is considered as the best standard therapy at the moment, will have relapsed within 2 years. We propose to compare the progression-free survival of patients treated with multiple sequential high dose chemotherapy or standard chemotherapy. The best results are likely to be observed in patients with small volume residual disease after surgery. A large improvement in progression-free survival in this favourable prognostic group is needed if high dose chemotherapy is to be considered a step forward in the treatment of advanced ovarian cancer.

3. OBJECTIVES

3.1 PRIMARY OBJECTIVE

To compare the progression-free survival of patients undergoing high dose sequential chemotherapy compared with conventional chemotherapy for optimally debulked stage III and IV ovarian cancer.

3.2 SECONDARY OBJECTIVE

Overall survival, toxicity of treatment and quality of life in the two groups.

4. PATIENT SELECTION

4.1 INCLUSION CRITERIA

Patients must fulfil **all** the following criteria to be eligible for the study:

1. Histologically proven FIGO stage III or IV epithelial ovarian cancer or carcinoma of the fallopian tubes (Appendix 1).

2. Bilateral salpingo-oophorectomy, hysterectomy and omentectomy with **less than 2 cm tumour (maximum diameter) remaining**.

3. Patients must be aged ≥ 18 and ≤ 65 years old.

4. Patients must have ECOG Performance Status 0, 1 or 2 (Appendix 2).

5. No previous chemotherapy or radiotherapy

6. Patients must be medically fit for high dose chemotherapy and have no uncontrolled concurrent serious medical illness, including hearing problems. Creatinine clearance/GFR greater than 60 ml/minute.

7. Patients must have given written and informed consent to the study.

8. Chemotherapy must commence within 6 weeks of surgery.

4.2 EXCLUSION CRITERIA

Patients with one or more of the following **will not** be eligible for the study.

1. Patients with a prior concomitant malignancy other than basal cell carcinoma of the skin or in situ neoplasia of the cervix uterii, diagnosed in the last 5 years.

2. Patients with active cardiac disease or other serious medical problem.

3. Patients with incompletely resected carcinoma of the ovary. Residual masses greater than 2 cm in maximum diameter.

5. TREATMENT PROCEDURES

Patients will be randomly assigned to one of two treatment arms:

➡ **Arm A** sequential high dose chemotherapy

5 cycles of treatment will be given with peripheral blood stem cell harvesting performed after cycle 1. (Additional stem cell harvesting may be performed after cycle 2 if yield inadequate - see Appendix 3). Cycles 3, 4 and 5 will be supported by peripheral blood stem cells. All cycles will be supported by filgrastim.

➡ **Arm B**, standard chemotherapy

Patients will receive 6 cycles of chemotherapy at 3 week intervals

5.1 TRIAL ARM A: SEQUENTIAL HIGH DOSE CHEMOTHERAPY

Cycle 1

Day 1 *Suggested premedication for paclitaxel*. Dexamethasone 20 mg po 12 and 6 hours before paclitaxel or dexamethasone 8 mg (minimum) i.v. 30 minutes before paclitaxel.
Chlorpheniramine 10 mg i.v.
Ranitidine 50 mg i.v. (or cimetidine 400 mg)

- **Paclitaxel** 200 mg/m^2 in 500 ml 5% Dextrose over 3 hours.
  Prehydration: 1000 ml 0.9% saline over 2 hours.
- **Cyclophosphamide** 3 g/m^2 in 500 ml 0.9% saline over 2 hours with 1.5 g Mesna.
  Posthydration: 1000 ml 0.9% saline with 3 g/m^2 Mesna over 12 hours.

GCSF (filgrastim) 5 µg/kg sc daily, starting 24 hours after chemotherapy until stem cell harvest. (suggested dose 300µg if <80kg, 480µg if >80kg) (see Appendix 3).

Cycle 2

As per Cycle 1. A further collection of stem cells may be performed if an insufficient number were harvested after cycle 1. filgrastim as per cycle 1.

Cycle 3 and 4

Day 1 *Suggested premedication for paclitaxel*. Dexamethasone 20 mg po 12 and 6 hours before paclitaxel or dexamethasone 8 mg (minimum) i.v. 30 minutes before paclitaxel.
Chlorpheniramine 10 mg i.v.
Ranitidine 50 mg i.v. (or cimetidine 400 mg)

- **Paclitaxel** 200 mg/m^2 in 500 ml 5% Dextrose over 3 hours.
  Prehydration: 1000 ml 0.9% saline over 2 hours.
- **Carboplatin** AUC 20 (see Appendix 4) in 500 ml 5% Dextrose over 4 hours.
  Posthydration: 1000ml 0.9% saline with 20 mmol KCl over 8 hours twice.

➡ **Peripheral blood stem cells returned 72 hours after carboplatin.**

Note: An EDTA GFR must be performed and new carboplatin dose calculated if the serum creatinine is >1.3mg/dl or 130µmol/l before proceeding with the next cycle.

Cycle 5

Day 1 *Suggested Premedication for paclitaxel*. Dexamethasone 20 mg po 12 and 6 hours before paclitaxel or dexamethasone 8 mg (minimum) i.v. 30 minutes before paclitaxel.
Chlorpheniramine 10 mg i.v.
Ranitidine 50 mg i.v. (or cimetidine 400 mg)

- **Paclitaxel** 200mg/m^2 in 500ml 5% Dextrose over 3 hours.
  Prehydration: 1000ml 0.9% saline over 2 hours.
- **Carboplatin** AUC 20 (see Appendix 4) in 500ml 5% Dextrose over 4 hours.
  Posthydration: 1000 ml 0.9% saline with 20 mmol KCl over 8 hours twice.

Day 2

- **Melphalan** 140mg/m^2 in 250 ml 0.9% saline over 15 minutes.
  Posthydration: 1000 ml 0.9% saline with 20 mmol KCl over 6 hours twice.

Peripheral blood stem cells returned 72 hours after carboplatin (melphalan may be give on Day 3 but at least 24 hours must elapse before return of PBSC).

5.1.2 Filgrastim support post chemotherapy

Cycles 3, 4 & 5

GCSF (filgrastim) 5µg/kg per day (normal dose 300µg or 480µg if >80kg) should be given after each course of peripheral blood stem supported chemotherapy starting day 1 (i.e. the day after return of PBSC) and ending when the neutrophil count reaches 0.5 x 10^9/L on two days or ≥ 1.0 x 10^9/L on one day.

Cycles of treatment should be given every 3-4 weeks where ever possible. The reasons for delaying treatment beyond 4 weeks must be clearly stated.

A greater than 6 week delay between treatment cycles will constitute a withdrawal from the study.

5.2 TRIAL ARM B: STANDARD CHEMOTHERAPY

Trial Arm B

The treatment recommended is 6 cycles of **carboplatin** AUC 5 and **paclitaxel** 175mg/m^2 over 3 hours; at 3 week intervals

Cisplatin 75mg/m^2 maybe substituted for carboplatin in centres declaring this to be standard therapy. Centres who wish to add an anthracycline (doxorubicin or epirubicin) must indicate **before randomisation** the standard arm drugs and dosage they intend to use. Treatment cycles with drugs containing anthracyclines should be at 4-week intervals.

6. INVESTIGATIONS

6.1 PRE-TREATMENT INVESTIGATIONS

1. Chest radiograph.

2. CT scan of abdomen and pelvis post-surgery.

3. Full blood count.

4. Urea, creatinine, electrolytes, bilirubin, AST (SGOT), Alkaline phosphatase.

5. Serum CA 125.

6. EDTA GFR or creatinine clearance.

7. Electrocardiogram.

Additional investigations for patients entering the high dose arm (A):

8. Audiogram.

9. Hepatitis B and C serology.

6.2 INVESTIGATIONS DURING TREATMENT

Routine haematological and biochemical tests will be taken during treatment. The frequency will be determined by the investigator's usual practice. It is recommended that a serum CA125 is taken prior to each cycle of chemotherapy.

6.3 INVESTIGATIONS AT THE END OF TREATMENT

1. Full blood count

2. Blood chemistry

3. Liver function tests

4. Serum CA 125

5. Chest radiograph (if previously abnormal)

6. CT scan of the abdomen and pelvis three months after treatment ends.

Additional investigations for study Arm A (high dose therapy)

7. GFR (3 months after the completion of therapy)

8. Audiogram (3 months after completion of treatment)

7. RANDOMISATION

To enter a patient, please complete the study specific randomisation form and fax it to the EBMT Central Office in London.

Fax: +44 (0)20 580 7580 / Tel: +44 (0)20 7380 9317

8. ADVERSE EVENTS

8.1 NON-HAEMATOLOGICAL TOXICITY

Toxicity (grade 3 or 4) should be recorded using the NCI common toxicity criteria in Appendix 10.

8.2 SERIOUS ADVERSE EVENTS

A serious adverse event is defined as any event that suggests a significant hazard or side effect, regardless of the investigators opinion on the relationship to study drugs. This includes, but may not be limited to, to the following (at any dose):

- Death regardless of cause occurring during treatment or within 30 days of the last dose of chemotherapy, or after 30 days, if death is a result of delayed toxicity due to administration of chemotherapy.
- Life threatening events. These are, in the view of the investigator, defined as events where the patient is at immediate risk of death.
- A permanently disabling event.
- Prolonged hospitalisation defined as continued inpatient care more than 14 days following the recovery of stable unsupported blood counts (neutrophil count greater than 1.0 x 10^9/L, platelet count greater than 20 x 10^9/L).

All serious adverse events should be reported by fax to the EBMT Central Office in London within 72 hours.

9. DISCONTINUATION OF STUDY

Patients may withdraw at their request from the study at any time. They may be withdrawn by the investigator if the toxicity is considered to be excessive, or there is evidence of disease progression while on treatment. An excessive delay between cycles of treatment (greater than 6 weeks) will lead to a withdrawal of the patient from the study.

The analysis will be performed on an intention to treat basis and all patients randomised will be included for analysis.

10. FOLLOW UP

Progression-free survival is the primary end point of this study. It has been agreed that a second-look operation will not be performed to define relapse.

Relapse is defined by clinical and/or radiological progression.

The recommended follow up programme consists of:

- 3-monthly CA 125 measurements.
- Clinical assessment, including gynaecological examination.
- Imaging: CT scan of abdomen and pelvis 3 months after end of chemotherapy and thereafter if clinically indicated or triggered by a rising CA 125.

If the CA125 is raised above the upper limit of normal it should be repeated monthly.

When the CA 125 is ≥ twice the upper limit of normal it should be repeated 3-4 weeks later. If it is still ≥ twice the upper limit of normal the patient has probably relapsed (Rustin et al[22], see Appendix 5). Clinical examination and a CT scan of the abdomen and pelvis should be performed. Approximately 10% patients will relapse without elevation in CA125. In such cases clinical/radiological criteria will be used.
If the clinical examination and CT scan are normal they should be repeated at 3 monthly intervals as relapse will occur. No further chemotherapy should be given until relapse has been confirmed and the date of relapse is defined by the first positive CT scan or clinical examination.

Follow up forms need to be completed 3-monthly for 2 years. Patients should then be seen at least 6-monthly up to 5 years. An annual form will be requested from year 5 onwards to obtain long term follow up data.

11. QUALITY OF LIFE ASSESSMENT

Toxicity and acceptability of treatment are important components of this study.

The EORTC QL C-30 will be used at the following time-points:

- Pre-treatment:
  - Baseline
- Post-treatment:
  - 4 - 6 weeks after last chemotherapy
  - 3, 9 and 15 months post chemotherapy

12. STATISTICAL CONSIDERATIONS AND INTERIM ANALYSES

We estimate the progression-free survival to be about 35 % at two years with conventional treatment (arm B)[4, 23]. In order to be able to detect an absolute difference of 15% in progression free survival at this time point, with a power of 80% and an alpha value of 5% using a 1-tailed test (according to the one-sided nature of the research question) 208 patients need to be recruited into the trial in a fixed sample design. The sample size is based on the expected rate of patient recruitment and a requirement of a minimum follow-up of at least two years or up to progression.

A group sequential analysis with an O'Brien/Fleming boundary shape will be adopted for the trial with interim analyses performed at approximately yearly intervals, the exact frequency depending on accrual and event rates. An independent Data Monitoring Committee (DMC) will review the interim analyses.

13. REGULATORY AND ETHICAL CONSIDERATIONS

This trial is open to centres with experience in high dose chemotherapy and peripheral blood stem cell transplantation. The support procedures for patients undergoing therapy (febrile neutropenia, blood and platelet transfusion) are to be defined by local practice.
It is the responsibility of each centre to ensure that ethics committee approval for the study has been granted.
Additional local regulatory requirements to cover indemnity should be discussed with Kim Champion at the EBMT Central Office in London, who will help to support the acquisition of such approval.

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J Clin Oncol 1989; 7 : 1748-1756.

15. APPENDICES

APPENDIX 1 - FIGO STAGE

I Growth limited to the ovaries

IA Growth limited to one ovary; no ascites. No tumour on the external surface, capsule intact.

IB Growth limited to both ovaries; no ascites. No tumour on the external surface, capsule intact.

IC* Tumour either Stage IA or IB but with tumour on the surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings.

II Growth involving one or both ovaries with pelvic extension

IIA Growth involving one or both ovaries with pelvic extension.

IIB Extension and/or metastases to the uterus and/or tubes.

IIC* Tumour either Stage IIA or IIB but with tumour on the surface of one or both ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings.

III Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equal Stage III. Tumour is limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum.

IIIA Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.

IIIB Tumour of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative.

IIIC Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.

IV Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytologic test results to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV.

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* To evaluate the impact on prognosis of the different criteria for allotting cases to Stage IC or IIC, it would be of value to know if rupture of the capsule was (1) spontaneous or (2) caused by the surgeon, and if the source of malignant cells detected was (1) peritoneal washings or (2) ascites.

APPENDIX 2 - ECOG

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)
PERFORMANCE STATUS SCALE

ECOG Scale	Performance Status
0	Fully active, able to carry out all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair.
5	Dead.

NOTE THAT:

ECOG 0	corresponds to Karnofsky performance status of	100 - 90
ECOG 1	corresponds to Karnofsky performance status of	80 - 70
ECOG 2	corresponds to Karnofsky performance status of	60 - 50
ECOG 3	corresponds to Karnofsky performance status of	40 - 30
ECOG 4	corresponds to Karnofsky performance status of	20 - 10
ECOG 5	corresponds to Karnofsky performance status of	0

APPENDIX 3 - PERIPHERAL BLOOD STEM CELL HARVEST

Peripheral blood stem cell harvest will be performed after the first cycle of treatment in patients allocated to the high dose arm (Arm A).

- Normally, leukapheresis will be performed 10 days after the first cycle or when the WBC $\geq 1.0 \times 10^9$/l.
- Between 1-3 leukaphareses sessions will be required to obtain a minimum of 4×10^6/kg CD34 positive cells (CD34+).
- It is strongly suggested that a minimum of 6×10^6/kg CD34+ cells are collected so that they can be stored in 3 batches of 2×10^6/kg CD34+ aliquots.
- A minimum of $1x\ 10^6$/kg CD34+ cells should be given with the first two high dose chemotherapy treatments (cycles 3 and 4) and $\geq 2x\ 10^6$/kg CD34+ cells after the last cycle (cycle 5).
- It is recommended that 2×10^6/kg CD34+ cells should be returned with each high dose cycle. Patients with less than the total required minimum number of CD34+ cells may proceed to a second leukapheresis after cycle 2.

APPENDIX 4 - CARBOPLATIN DOSE CALCULATION

The dose of carboplatin is calculated from the glomerular filtration rate (GFR) ml/min. Carboplatin clearance is linearly related to GFR and the target dose, given as the area under the concentration time curve, (AUC) is:

Total Dose (mg) = Target AUC x (GFR + 25)

See Calvert AH, Newell DR, Gumbrell et al[24]. GFR is most accurately calculated by the ^{51}CrEDTA clearance and this is recommended. Where this investigation cannot be performed, the creatinine clearance can be used. The latter correlates closely with the ^{51}CrEDTA method in patients prior to cisplatin therapy but does not correlate closely once patients have received cisplatin.

The first calculated carboplatin dose with AUC20 shall be maintained for all three high dose cycles unless the serum creatinine rises above 1.3 mg/dl or 130µmol/l (page 10). In such a case a new calculation of the carboplatin dose should be made on an actual ^{51}CrEDTA clearance.

APPENDIX 5 - PROGRESSION OF OVARIAN CANCER

Raised serum CA125 levels are found in more than 85% of patients with active ovarian cancer. Rustin et al (1996) have used serum CA125 to define progression of ovarian cancer based on serial estimations of CA125.

In a prospective study Rustin et al[22] defined progression as a doubling of CA125 from the upper limit of normal. Using this method the sensitivity was 85.9%, specificity 91.3% and positive predictive value 94.8%. The negative predictive value was 77.8%. With a confirmatory level the false positive rate was <2% with a sensitivity of 83.9%.

- CA125 should be measured 3-monthly during the first 24 months of follow-up.
- If the CA125 is raised above the upper limit of normal it should be repeated monthly.
- When the CA125 is ≥ twice the upper limit of normal and confirmed by a further sample 3-4 weeks later there is a high probability that the patient has relapsed.

At this point a clinical and CT assessment should take place. Relapse is defined only if either of these are positive. CT scans should be repeated at 3 monthly intervals until relapse has been confirmed. The date of relapse is defined as the first date that either clinical examination or imaging is positive.

APPENDIX 6 - EORTC-QL-C30

Name: Trial number:

Hospital number: Date completed:

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	No	Yes
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2. Do you have any trouble taking a long walk?	1	2
3. Do you have any trouble taking a short walk outside of the house?	1	2
4. Do you have to stay in a bed or a chair for most of the day?	1	2
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2

During the past week:

	Not at all	A little	Quite a bit	Very much
6. Were you limited in any way in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go to the next page

During the past week:

	Not at all	A little	Quite a bit	Very much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhoea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social life?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7
Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7
Very poor Excellent

A RANDOMISED PHASE III TRIAL OF SEQUENTIAL HIGH DOSE CHEMOTHERAPY OR STANDARD CHEMOTHERAPY FOR OPTIMALLY DEBULKED FIGO STAGE III AND IV OVARIAN CANCER

Patient Information Sheet

You have been advised to have chemotherapy following surgery for ovarian cancer. Chemotherapy for ovarian cancer has changed over the years as new drugs have become available. These changes have improved the outcome of ovarian cancer but better treatments are still needed.

One approach is to use much higher doses of the drugs that we know are active in ovarian cancer to try to prevent tumour cells from becoming resistant to chemotherapy. This can now be done by storing cells, called stem cells, from your blood which can be returned to you to help you recover from the side effects of chemotherapy more quickly. This technique is called peripheral stem cell transplantation. It is being widely used in cancer treatment and for some cancers this treatment has been shown to improve survival. Preliminary work carried out in ovary cancer suggests this type of treatment may be a step forward. The only way to find out if this is true is by performing a randomised clinical trial. In such a trial patients are randomly allocated either to the best known standard treatment or to the new treatment, and after many patients have been treated it is possible to compare the two treatments.

What would be involved?
If you decide to enter the trial you would be allocated either to high dose treatment or a standard therapy containing a combination of drugs that are currently regarded as the standard treatment. If you are receiving the new treatment you would have stem cells collected after the first cycle of therapy. Treatment would be given through a central venous line (sometimes called a Hickman line) that is inserted into a vein that lies beneath your collarbone under a local or brief general anaesthetic. This would provide venous access for all your therapy. Daily injections of a hormone (growth factor) [G-CSF] to stimulate blood cell production would be given into the skin, similar to diabetic patients given insulin, for about ten days. Stem cells would be taken off by removing blood and returning it to you after passing the cells through a cell separator. This would take a few hours on one to three days, depending on how many cells are collected. It will be necessary to put in an extra intravenous drip line to take off the blood. Four cycles of chemotherapy would be given as an inpatient. The blood stem cells would be returned after the 3rd, 4th and 5th cycle of treatment (like a blood transfusion). Further injections of G-CSF would be given after each cycle to accelerate the recovery of blood counts. As the treatment is more intensive patients will need to stay in for a few days after each course. The length of hospital stay will depend on the side effects of treatment which are explained in the next section. The details of treatment are given at the end of this information sheet.

Standard therapy is usually given in the day care unit by an intravenous infusion lasting about 4 hours, every three weeks. Six cycles of treatment will be given.

What are the side effects of treatment?
The main side effects of the standard treatment are hair loss and possibly nausea and vomiting. One of the drugs, paclitaxel, can sometimes cause an aching in the limbs and rarely damage to the nerve endings. The side effects of high dose therapy will be greater. In addition to the side effects of the standard treatment, you may develop a sore mouth and symptoms of infection if the white blood cell count is very low. The platelets (cells that prevent bruising and bleeding) may also fall and platelet transfusions may be necessary. During the final 5th cycle of chemotherapy you will need a much longer period in hospital as the additional drug

melphalan may cause a sore mouth with ulcers. Intravenous fluids are likely to be needed until this recovers. The unit treating you has considerable experience in managing this type of treatment, which is being used in many patients with other types of cancer. Rarely, the side effects of treatment can be severe and very occasionally life threatening. We would expect a full long-term recovery from chemotherapy but we would need to see you at regular intervals after both standard and intensive treatment in the clinic.

We hope that the new intensive treatment will improve the survival of patients with ovarian cancer. This will only become clear after the trial has been completed. It is important that a new treatment is acceptable to patients and we would therefore like you to complete 'quality of life' forms periodically that tell us how you are feeling and what activities you are able to perform.

You have no obligation to join this study. If you do, you will be randomly assigned intensive or standard treatment. It is important that neither you nor your doctor choose the type of treatment as this may introduce bias into the results. If you decide not to enter the trial your doctor will probably advise standard treatment, or an alternative if this is unacceptable to you. You can withdraw from the study at anytime without reason, and this will not affect your future care.

For further information please discuss the trial with .....

DETAILS OF TREATMENT

High dose treatment

Cycle 1

Cyclophosphamide/paclitaxel
Collection of peripheral blood stem cells (PBSC)
G-CSF

↓

Cycle 2

Cyclophosphamide/paclitaxel
(Possible further collection of PBSC)
G-CSF

↓

Cycle 3

Carboplatin/paclitaxel
Return of PBSC
G-CSF

↓

Cycle 4

Carboplatin/paclitaxel
Return of PBSC
G-CSF

↓

Cycle 5

Carboplatin/paclitaxel/melphalan
Return of PBSC
G-CSF

? Cycles at 3-4 week intervals

Standard treatment

Cycle 1

Carboplatin/paclitaxel

↓

Cycle 2

Carboplatin/paclitaxel

↓

Cycle 3

Carboplatin/paclitaxel

↓

Cycle 4

Carboplatin/paclitaxel

↓

Cycle 5

Carboplatin/paclitaxel

↓

Cycle 6

Carboplatin/paclitaxel

? Cycles at 3 week intervals

APPENDIX 9 - CONSENT FORM

A RANDOMISED PHASE III TRIAL OF SEQUENTIAL HIGH DOSE CHEMOTHERAPY OR STANDARD CHEMOTHERAPY FOR OPTIMALLY DEBULKED FIGO STAGE III AND IV OVARIAN CANCER

Consent Form

The proposed study has been explained to me by ..... and I have been given a copy of the Information Sheet.

I have had sufficient time to consider the trial and other treatments, and have been given the opportunity to ask questions about the study.

I, ..., agree to participate in the trial and understand that I may choose to withdraw from the study at any time, without reason, and that my future care will be unaffected by this decision.

Signed: .....

Date: .....

Witness: .....

Date: .....

APPENDIX 10 - SUGGESTED LETTER TO THE GENERAL PRACTITIONER

Dear Dr

RE:

Your patient has undergone surgery for FIGO Stage III or IV ovarian cancer and has agreed to participate in a randomised trial of sequential high dose vs standard dose chemotherapy, run by the European Group for Blood and Marrow Transplantation (EBMT) in collaboration with the German AGO/AIO and the French GINECO study groups. The study has been approved by the Local Research Ethics Committee. Your patient has been allocated to receive

In the standard arm, six cycles of carboplatin and paclitaxel will be administered. The high dose arm is supported by peripheral blood stem cell support. The patient has been given a full explanation about the treatment and its side effects and has an information leaflet. If you have any questions or concerns please do not hesitate to contact me.

Yours sincerely,

APPENDIX 11 - TOXICITY CRITERIA

Modified NCI Common Toxicity Criteria

Modified NCI Toxicity	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
AL LER Allergy	none	transient rash, fever <38°C, 100.4°F	Urticaria, fever = 38°C, 100.4°F, mild bronchospasm	serum sickness, bronchospasm, req parenteral meds	anaphylaxis
	Fever felt to be caused by drug allergy should be coded as ALLERGY (AL LER). Non-allergic drug fever (eg: as from biologies) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to infection, code INFECTION only (IN FEC or IN NEU). NB: Protocols requiring detailed reporting of hypersensitivity reactions will include a Hypersensitivity Reaction module.				
BLOOD / BONE MARROW (SI Units)					
BL WBC White Blood Count (WBC)	>4.0 x 10^9/l	3.0 – 3.9	2.0 - 2.9	1.0 - 1.9	<1.0
BL PLT Platelets	WNL x 10^9/l	75 - normal	50.0 – 74.9	25.0 – 49.9	<25.0
BL HGB Hemoglobin	WNL g/l	100 - normal	80 - 99	65 - 79	<65
BL GRA Granulocytes (ie neuts + bands)	>2.0 x 10^9/l	1.5 -1.9	1.0 – 1.4	0.5 – 0.9	<0.5
BL LYM Lymphocytes	>2.0 x 10^9/l	1.5 -1.9	1.0 – 1.4	0.5 - 0.9	<0.5
BL HEM Hemorrhage resulting from thrombocyto-penia (clinical)	none	mild, no transfusion (incl bruise/ hematoma, petechiae)	gross,1-2 units transfusion per episode	gross, 3-4 units transfusion per episode	massive, >4 units transfusion per episode
BL OTHER Other*	none	mild	moderate	severe	life threatening
CARDIOVASCULAR					
CD VEN Venous*	none	superficial (excl IV site reaction-code SK LTO)	deep vein thrombosis not req anticoagulant therapy	deep vein thrombosis req anticoagulant therapy	pulmonary embolism
CD DYS Dysrhythmias	none	asymptomatic, transient, req no therapy	recurrent or persistent, no therapy req	req trt	req monitoring, or hypotension, or ventricular tachycardia, or fibrillation
CD EDE Edema* (eg peripheral edema)	none	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalised anasarca
CD FUN Function	none	asymptomatic, decline of resting ejection fraction of > 10% but < 20% of baseline value	asymptomatic, decline of resting ejection fraction by>20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
CD ISC Ischemia (myocardial)	none	non-specific T wave flattening	asymptomatic, ST &T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
CD PER Pericardial	none	asymptomatic, effusion, no intervention req	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage req	tamponade, drainage urgently req; or constrictive pericarditis req surgery

Modified NCI Toxicity	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
CD OTH Other*	none	mild	moderate	severe	life threatening
COAGULATION					
CG FIB Fibrinogen	WNL	0.99-0.75 x N	0.74-0.50 x N	0.49-0.25 x N	<0.24 x N
CG PT Prothrombin time	WNL	1.01-1.25 x N	1.26-1.50 x N	1.51-2.00 x N	>2.00 x N
CG PTT Partial thromboplastin time	WNL	1.01-1.66 x N	1.67-2.33 x N	2.34-3.00 x N	> 3.00 x N
CG OTH Other*	none	mild	moderate	severe	life threatening
FLU-LIKE SYMPTOMS					
FL FEV Fever in absence of infection* (incl drug fever)	none	37.1 – 38.0 °C 98.7 – 100.4 °F	38.1 – 40.0 °C 100.5 – 104.0 °F	>40.0°C >104.0 °F for <24hrs	>40.0°C (104.0°F) fir >24hrs or fever accompanied by hypotension
Fever felt to be caused by drug allergy should be coded as ALLERGY (AL LER). Non-allergic drug fever (eg: as from biologics) should be coded under FLU-LIKE SYMPTONS (FL FEV). If fever is due to infection, code INFECTION only (IN FEC or IN NEU)					
FL JOI Arthralgia* (joint pain)	none	mild	moderate	severe	–
FL MYA Myalgia* (muscle ache)	none	mild	moderate	severe	–
FL OTH Other *	none	mild	moderate	severe	life threatening
GASTROINTESTINAL					
GI ASC Ascites (non-malignant)*	none	mild	moderate	severe	life threatening
GI DIA Diarrhea	none	increase of 2-3 stools/day; or mild increase in loose watery colostomy output compared to pre-trt	increase of 4-6 stools/day, or nocturnal stools; or moderate increase in loose watery colostomy output compared to pre-trt	increase of 7-9 stools/day, or incontinence, malabsorption; or severe increase in loose watery colostomy output compared to pre-trt	increase of >10 stools/day, or grossly bloody diarrhea; or grossly bloody colostomy output or loose watery colostomy output req parenteral support; dehydration
GI DPH Esophagitis/ dysphagia/ odynophagia* (incl recall reaction)	none	dys. or odyn. not req trt, or painless ulcers on esophagoscopy	dys. or odyn. req trt	dys. or odyn. lasting > 14 days despite trt	dys. or odyn with 10% loss of body wt, dehydration, hosp. req
GI HEM Gastrointestinal bleeding*	none	mild, no transfusion	gross, 1-2 units transfusion per episode	gross, 3-4 units transfusion per episode	massive, >4 units transfusion per episode
Bleeding resulting from thrombocytopenia should be coded under BL HEM, not GI					
GI NAU Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	–

Modified NCI Toxicity	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
GI OBS Small bowel obstruction*	none	–	intermittent, no intervention	req intervention	req operation
GI STO Stomatitis / oral	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema, edema, or ulcers, and cannot eat	mucosal necrosis and/or req parenteral or enteral support, dehydration
GI ULC Gastritis / ulcer*	none	antacid	req vigorous medical management or non-surgical trt	uncontrolled by medical management; req surgery for GI ulceration	perforation or bleeding
GI VOM Vomiting	none	1 episode in 24hrs	2-5 episodes in 24 hrs	6-10 episodes in 24hrs	>10 episodes in 24hrs or req parenteral support, dehydration
GI OTH Other*	none	mild	moderate	severe	life threatening
GENITOURINARY					
GU BLA Bladder changes*	none	light epithelial atrophy, or minor telangiectasia	generalised telangiectasia	severe generalised telangiectasia (often with petechiae) or reduction in bladder capacity (<150ml)	necrosis, or contracted bladder (capacity <100ml), or fibrosis
GU CRE Creatinine	WNL	<1.5 x N	1.5 – 3.0 x N	3.1-6.0 x N	>6.0 x N
GU CYS Cystitis* (non-bacterial)	none	mild symptoms req no intervention	symptoms relieved completely with therapy	symptoms not relieved despite therapy	severe (life threatening)cystitis
Urinary tract infection should be coded under infection, not GU					
GU HEM Hematuria, bleeding per vagina	neg	micro only	gross, no clots	gross + clots	req transfusion
Bleeding resulting from thrombocytopenia should be coded under BL HEM not GU					
GU PRT Proteinuria	no change	1+ or <0.3g% or <3g/L	2.3+ or 0.3-1.0 g% or 3-10g/L	4+ or >1.0g% or >10g/L	nephrotic syndrome
GU OTH Other	none	mild	moderate	severe	life threatening
HEPATIC					
HP ALK Alk Phos or 5' nucleotidase	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP ALT Transaminase SGPT (ALT)	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP AST Transaminase SGOT (AST)	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP BIL Bilirubin	WNL	-	<1.5 x N	1.5-3.0 x N	>3.0 x N
HP CLI Liver (clinical)	no change from baseline	-	-	precoma	hepatic coma
HP LDH LDH*	WNL	<2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N

Modified NCI Toxicity	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
HP OTH Other*	none	mild	moderate	severe	life threatening
Viral Hepatitis should be coded as infection rather than liver toxicity					
INFECTION					
IN FEC Infection	none	mild, no active trt	moderate, localised infect req active trt	severe, systemic infect req parenteral trt, specify site	life threatening sepsis, specify site
IN NEU Febrile neutropenia* Absolute gran. count <1.0 x 10^9/L, fever > 38.5^{o}C treated with (or ought to have been treated with) IV antibiotics	none	–	–	present	–
Fever felt to be caused by drug allergy should be coded as ALLERGY (AL LER). Non-allergic drug fever (eg as from biologies) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to infection, code INFECTION only (IN FEC or IN NEU)					
METABOLIC (SI UNITS)					
MT AMY Amylase	WNL	<1.5 x N	1.5-2.0 x N	2.1-5.0 x N	>5.1 x N
MT LCA Hypocalcemia	>2.10 mmol/L	2.10-1.93	1.92-1.74	1.73 – 1.51	≤1.50
MT LKA Hypokalemia*	no change or >3.5 mmol/L	3.1-3.5	2.6-3.0	2.1-2.5	≤2.0
MT LMA Hypomag-nesemia	>0.70 mmol/L	0.70-0.58	0.57-0.38	0.37-0.30	≤0.29
MT LNA Hyponatremia*	no change or >135 mmol/L	131-135	126-130	121-125	≤120
MT OTH Other*	none	mild	moderate	severe	life threatening
NEUROLOGIC					
NE CER Cerebellar	none	slight incoordination, dysdiadocho-kinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
NE CON Constipation	none or no change	mild	moderate	severe, obstipation	ileus > 96hrs
NE COR Cortical (incl drowsiness)	none	mild somnolence	moderate somnolence	severe somnolence, confusion, disorientation, hallucinations	coma, seizures, toxic psychosis
NE HER Altered hearing	none or no change	asymptomatic, hearing changes on audiometry only	tinnitus, symptomatic hearing changes not req hearing aid or trt	hearing changes interfering with function but correctable with hearing aid or trt	hearing changes or deafness not correctable
NE MOT Motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis

Modified NCI Toxicity	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
NE SEN Sensory	none or no change	mild paresthesias, loss of deep tendon reflexes (incl tingling)	mild or moderate objective sensory loss; moderate paresthesias	sensory loss or paresthesias that interfere with function	–
NE OTH Other*	none	mild	moderate	severe	life threatening
OTHER					
OT OTH Other	none	mild	moderate	severe	life threatening
For toxicities which do not have an existing code, but do fit into an existing toxicity category, use 'other' variable in the appropriate toxicity category. Only toxicities which do not fit into existing categories should be coded OTHER OTHER (OT OTH).					
PULMONARY					
PU COU Cough*	none	mild	moderate	Severe	–
PU EDE Pulmonary Edema*	none	–	out-pt management	in-pt management	req. intubation
PU FIB Pulmonary Fibrosis*	normal	radiographic changes, no symptoms	–	Changes with symptoms	–
PU PNE Pneumonitis* (non-infectious)	normal	radiographic changes, symptoms do not req steroids	steroids req	oxygen req	req. assisted ventilation
PU SOB Shortness of breath (SOB) (incl wheezing)	none or no change	asymptomatic, with abnormality in PFT's	dyspnea on significant exertion	dyspnea at normal level of activity, apnea without cyanosis	dyspnea at rest, apnea with cyanosis
PU OTH Other*	none	mild	moderate	severe	life threatening
SKIN					
SK ALO Alopecia	no loss	mild hair loss	pronounced or total head hair loss	total body hair loss	–
SK DES Desquamation*	none	dry desquamation	moist desquamation	confluent moist desquamation	–
SK RAS Rash/Itch* (not due to allergy) (incl recall reaction)	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symtoms	generalised symptomatic macular, papular, or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
SK OTH Other*	none	mild	moderate	severe	life threatening
WEIGHT					
WT GAI Weight Gain	<5.0%	5.0-9.9%	10.0-19.9%	>20.0%	–
WT LOS Weight Loss	<5.0%	5.0-9.9%	10.0-19.9%	>20.0%	–

APPENDIX 11 - DECLARATION OF HELSINKI

ETHICAL GUIDELINES: THE DECLARATION OF HELSINKI

DECLARATION OF HELSINKI IV (Hong Kong - September 1989)

World Medical Association Declaration of Helsinki
Recommendations guiding physicians
in biomedical research involving human subjects.

Adopted by the 18th World Medical Assembly,
Helsinki, Finland, June 1964,
and amended by the
29th World Medical Assembly,
Tokyo, Japan, October 1975,
35th World Medical Assembly,
Venice, Italy, October 1983
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Hong Kong, September 1989.

1. Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

2. Basic Principles

2.1 Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2.2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

2.3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

2.4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

2.5 Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

2.6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

2.7 Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigations if the hazards are found to outweigh the potential benefits.

2.8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

2.9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that her or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

2.10 When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigations and who is completely independent of this official relationship.

2.11 In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

2.12 The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

3. Medical Research Combined With Professional Care (Clinical Research)

3.1 In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

3.2 The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3.3 In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.

3.4 The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

3.5 If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (See section 2.2).

3.6 The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

4. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-clinical biomedical research)

4.1 In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

4.2 The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

4.3 The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4.4 In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject